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Critical Review

Field size effects on the risk and severity of treatment-induced lymphopenia in patients undergoing radiation therapy for solid tumors

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Abstract

Purpose: Radiation-induced lymphopenia (RIL) is the result of direct toxicity to circulating lymphocytes as they traverse the irradiated field, occurs in 40% to 70% of patients who undergo conventional external beam radiation therapy, and is associated with worse outcomes in multiple solid tumors. As immunotherapy strategies evolve, a better understanding of radiation's effects on the immune system is needed in order to develop rational methods of combining RT with immunotherapy.

Methods and materials: This paper is a review of the available literature on the clinical significance and dosimetric predictors of radiation-induced toxicity to the immune system.

Results: An association between severe RIL and inferior survival has been described in multiple solid tumors, including glioma, lung cancer, and pancreatic cancer. RIL risk is correlated with field size, dose per fraction, and fraction number. SBRT and proton therapy techniques are associated with lower RIL risk.

Conclusions: The immune system should be considered an organ at risk during RT, and absolute lymphocyte count is an important biomarker of RT-induced immunotoxicity. Radiation dose and technique affect the risk and severity of RIL. Further research is needed to accurately characterize RT-induced immunotoxicity and develop strategies to prevent or mitigate this clinically significant side effect.

Introduction

Recent advances in immunotherapy have demonstrated the importance of the immune system in cancer control. Lymphocytes play a critical role in the anticancer immune response,[1] but are depleted by external beam radiation therapy (RT), which causes both acute and chronic lymphopenia. Because lymphocytes are one of the primary effector cells in the native immune response to cancer, and the action of the most efficacious immunotherapy agents (eg, checkpoint inhibitors) is mediated by lymphocytes, a logical mechanism links the depletion of these critical immune cells with poorer outcomes and a lower likelihood of response to immunotherapy.

The importance of the lymphocyte compartment in tumor-specific immune responses is illustrated by animal

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experiments that show that, unlike immunocompetent mice, T-cell deficient mice are unable to mount abscopal responses to a combination of RT and Flt-3 ligand enhancement.[2] Clinical reports of the abscopal effect also implicate tumor-antigen-specific cluster of differentiation (CD) 4 lymphocytes as a key mediator of the anticancer immune response, and have suggested that B lymphocytes may also play a role in the generation of humoral immune response to malignancies.[3] Therefore, lymphopenia can be intuitively proposed to diminish an individual's ability to mount a tumor-specific immune response.

Multiple recent studies have identified radiation-induced lymphopenia (RIL) as a negative prognostic factor in several treatment-refractory solid tumors, including high-grade glioma,[4–7] head and neck cancer,[8] non-small[9,10] and small cell lung cancer,[11] esophageal cancer,[12] resected[13] and unresectable[14] pancreatic cancer, and cervical cancer.[15] As summarized in Table 1, the risk and severity of RIL appears to be independent of steroid use or concurrent chemotherapy, because this toxicity occurs in 40% to 70% of patients treated with fractionated RT, regardless whether corticosteroid drugs or lymphotoxic chemotherapy agents are administered concurrently with RT. Early clinical data also suggest strongly that absolute lymphocyte count (ALC) is a biomarker of response to checkpoint blockade. Higher lymphocyte counts are associated with a higher response rate and more durable treatment response in patients treated with checkpoint inhibitors.[17]

RIL is likely caused by direct toxicity to circulating lymphocytes as they pass through the irradiated field, which suggests that circulating lymphocytes should be considered an organ at risk (OAR) during RT. The immunosuppressive effects of total body radiation that cause fatal bone marrow failure at even moderate doses are well described,[18] but those of focal fractionated radiation have not been as thoroughly studied, despite being of considerable clinical importance. As first observed in the early 20th century, when an area of tissue is irradiated, all circulating immune cells within the target and penumbra regions are also exposed to potentially lymphotoxic radiation doses.

A review article published in 1916 on the progress in the clinical application of RT noted not only that "the cells of the lymphoid tissue…readily succumb to the action of the rays," but also that "…every time we roentgenize any given area, we thereby also radiate the entire volume of blood" flowing through the targeted area while the beam is on.[19] Because lymphocytes are among the most radiosensitive cell types, the effects of irradiating

Table 1 Radiation-induced immunosuppression as a prognostic factor for survival in patients with solid tumors

Author	Primary site	Concurrent therapy	N	Immunosuppression measure	HR for death* (95% CI; *P*-value)
Grossman (2011)[7]	Glioma (high grade)	Temozolomide/ dexamethasone	96	ALC <500 2 months post-RT	1.8 (1.05-2.64; .03)
Mendez (2016)[5]	Glioblastoma	Temozolomide/ dexamethasone	76	ALC <500 2 months post-RT	2.8 (1.30-5.86; .008)
Rudra (2018)[4]	Glioblastoma	Temozolomide/ dexamethasone	210	ALC <500 at any time point post-RT	1.8 (1.20-2.80; .005)
Liu (2017)[8]	Nasopharynx	Cisplatin	413	Post-RT ALC nadir <390	1.8 (1.12-2.78; .015)
Davuluri (2016)[12]	Esophagus	5-FU (80%) Taxane (62%) Cisplatin (44%)	504	Post-RT ALC nadir <500	1.6 (1.05-2.37; .027)
Campian (2013)[9]	NSCLC	Carboplatin plus taxol (95%) or gemcitabine (5%)	47	ALC <500 2 months post-RT	1.7 (0.8-3.6; .17)
Tang (2014)[10]	NSCLC	Unspecified; 81% received chemotherapy	711	Post-RT ALC nadir	0.59† (0.37-0.95; .03)
Cho (2016)[11]	SCLC	Cisplatin/etoposide	73	Post-RT ALC nadir <297	2.7 (1.06-6.75; .038) 2.6 (1.19-5.74; .016)
Balmanoukian (2012)[13]	Pancreas	5-FU (76%) Gemcitabine (22%)	53	ALC <500 2 months post-RT	2.9 (1.53-5.41; .001)
Wild (2013)[14]	Pancreas	5-FU (59%) Gemcitabine (41%)	101	ALC <500 2 months post-RT	2.2 (1.17-4.12; .01)
Chadha (2017)[16]	Pancreas	Capecitabine (85%) Gemcitabine (13%)	177	Post-RT ALC nadir <200	1.7 (1.11-2.48; .01)
Cho (2016)[15]	Cervix uteri	Cisplatin	152	Post-RT ALC nadir <200	1.7

Abbreviations: 5-FU = 5-fluorouracil; ALC = absolute lymphocyte count; CI = confidence interval; HR = hazard ratio; NSCLC = non-small cell lung cancer; RT = radiation therapy; SCLC = small cell lung cancer.

* In lymphopenic versus nonlymphopenic patients.

† 50% increase in risk of death for each 1000 cells/μL decrement in ALC.

a large field at low doses are of considerable clinical importance. The linear shape of the lymphocyte cell survival curve after irradiation shows that exposure to even very low doses of radiation can cause lymphocyte cell death, because these cells lack the DNA repair capacity that is associated with the linear-quadratic kinetics of classic radiation survival curves in less radiation-sensitive cell types.[18,20]

This review provides a brief overview of existing evidence implicating the direct irradiation of circulating immune cells as the proximate cause of RIL, reviews contemporary studies on dosimetric parameters that have been found to be correlated with the risk and severity of radiation-induced lymphopenia, and suggests a theoretical framework to conceptualize the immune system as an OAR during radiation therapy. Of note, although radiation-induced immunosuppression is comprised of a wide spectrum of acute and chronic changes in lymphocyte subpopulations, cytokine expression patterns, and functional immune deficits (Table 2), its primary clinical manifestation is absolute lymphopenia. ALC is a clinically useful biomarker for several reasons, including its availability at the clinic and its strong correlation with survival in patients who receive RT, but additional research is needed to precisely and fully characterize the clinical syndrome of radiation-induced immunosuppression and identify additional immunologic biomarkers for response in patients who receive RT.

Historical perspective

The extreme radiation sensitivity of lymphocytes was noted by the earliest radiation therapists, who also identified the likely mechanism of radiation-induced lymphopenia: The irradiation of circulating immune cells as they pass through the treated area.[19] Later, investigators described the development of radiation-induced lymphopenia as well as functional immune deficits in patients with breast cancer,[35] pelvic tumors,[36] Hodgkin's lymphoma,[37] and other malignancies. The underlying pathophysiology of this phenomenon was revealed by a series of experiments that clearly demonstrated that irradiation of the circulating blood alone caused significant and durable lymphopenia.

For example, in 1962, Cronkite et al. reported a 60% drop in the peripheral ALC after extracorporeal irradiation of the circulating blood in calves.[38] Subsequent studies demonstrated immunosuppression that was sufficient to permit skin allograft acceptance in calves after extracorporeal blood irradiation alone.[39] In the late 1970s, attempts were made to translate these findings into humans. Weeke et al. reported on the utilization of extracorporeal blood irradiation for immunosuppression in renal allograft recipients.[40] Patients' circulating blood was irradiated by passing the blood under a cesium source embedded within a shielded dialysis unit during hemodialysis sessions. The shielding ensured that the patients themselves were not exposed to direct radiation from the cesium source. The degree of lymphopenia was directly proportional to the source strength and number of passes through the dialysis unit, which roughly corresponded to the dose per fraction and number of fractions in external beam treatment, respectively.

Additional evidence that implicated the circulating lymphocyte compartment as the main target organ for radiation-induced immune toxicity can be found in studies on the immunosuppressive effects of cranial radiation. Because the brain and skull contain little bone marrow or lymphoid tissue, the immunosuppressive effects of whole brain RT are probably due almost entirely to direct toxicity and circulating lymphocytes as they flow through the radiation field. This phenomenon was demonstrated conclusively in a cohort of pediatric patients who were treated with prophylactic cranial radiation for acute lymphocytic leukemia.[41] In that study, the total whole-brain radiation dose was held constant at 2400 to 2500 rads (24-25 Gy), but the number of fractions was left to the discretion of the treating physicians. Posttreatment ALC was inversely proportional to the number of fractions given, with each additional RT fraction resulting in an additional 5% to 6% reduction in the ALC at 3 months after the end of treatment.

Focal brain radiation also causes lymphopenia, as initially reported by Hughes et al. in a series on 76 patients with high-grade glioma who were treated with radiation and steroidal medications. In this cohort, 24% of patients were found to have CD4 counts <200 cells/μL by the end of RT.[42]

Summary of contemporary data: Field size and fractionation effects

On the basis of these historical observations, Yovino et al. postulated a basic method for the calculation of radiation dose received by circulating blood during a course of external beam RT.[43] This approach predicted that the circulating blood dose would depend on the fraction number, field size, and dose per fraction. The model was highly simplified and required several assumptions (which likely do not fully reflect physiologic conditions), including the following: 1) The target volume was spherical; 2) lymphocytes were homogeneously distributed throughout the target, flowed at uniform speed, and were equally radiation sensitive; 3) blood was the only structure within the target that contained circulating immune cells (ie, did not account for primary or secondary lymphoid structures); 4) there was no recirculation through the field while the beam was on; and 5) no lymphocyte repopulation occurred during treatment.

Table 2 Summary of RT effects on circulating lymphocyte subtypes

Author/year	N	Site	Technique	Markers/Time points	Findings
Maehata (2013)[21]	62	Lung	SBRT	CD3, CD4, CD8, CD19, CD56, NKA Baseline & weekly for 1st 4 weeks post RT	All subtypes down at 1 week post SBRT; CD3, CD4, CD19 only still down at 4 weeks
Rutkowski (2017)[22]	89	Lung	SBRT	T-bet, GATA-3, ROR-yT, FoxP3, CD4, CD8 Baseline and 2 weeks, 3 months post-RT	Decreased CD4:CD8 ratio at 2 weeks persisted at 3 months; reported % distribution only, not absolute numbers
Nakayama (1995)[23]	15	Lung	Conventional	CD3, CD4, CD8, CD45RA, CD56, CD20, CD11b+ Baseline and 2 weeks after RT	Decrease in all subsets except CD20, CD11b+; did not report CD4:CD8 ratio
Crocenzi (2016)[24]	20	Pancreas	Hypo- versus conventional fractionation	CD3, CD4, CD8, CD45, CD27, CD28, CD25, CD127 Baseline, 50, 100, 150, 200 days post day 1 of RT	Hypofractionated RT spared all studied subsets; conventional RT associated with decreased naïve:memory cell ratio whereas hypofractionated was not
Tabi (2010)[25]	12	Prostate	Hypo-fractionation	CD4, CD8, CD45RA, CD27 Baseline, Day 20 RT, 4 weeks post-RT	Decreased naïve T-cell populations
Yang (2016)[26]	19	Prostate	Carbon ion	CD4:CD8 ratio Baseline, after 10 fractions, last day of RT, 1 month post-RT	Higher post-RT CD4:CD8 ratio associated with higher complete and partial response rates
Van Meir (2016)[27]	30	Cervix uteri	EBRT + platinum	CD3, CD19, MDSC, PD-1, functional Baseline, daily during week 1, after 15 fx, 3, 6, 9 weeks post RT	Increase in relative proportion of MDSCs, decreased reactivity to immune stimuli, increased PD-1 expression
Santin (2002)[28]	15	Cervix uteri	EBRT/brachy +/- cisplatin	CD4:CD8 ratio, NK cells Baseline, week 5 of RT, 1 month post-RT	CD4:CD8 ratio higher in un-transfused patients; NK cell activity suppressed post-RT in both groups; RT + transfusion → anergy
Ellsworth (2014)[29]	12	Glioma	EBRT + TMZ	CD3, CD4, CD8, CD45RA, CD19, CD56, CD25, FoxP3 Baseline, 4 and 12 weeks post-RT	Nonsignificant decline in naïve:memory cell ratio; significant decline in CD4:CD8 ratio; relative sparing of CD8 and Tregs compared with CD4 and B cells
Fadul (2011)[30]	25	Glioma	EBRT + TMZ	CD3, CD4, CD8, Cd19, CD45RO, CD56, CCR7, CD25, CD45RA, CD14, CCR4, FoxP3, TEMRA Baseline, 4 weeks post-RT	Decreased CD3, CD4, CD56 populations; increased % of Tregs; decreased TEMRA cells; no change in naïve:memory ratios
Campian (2017)[31]	20	Glioma	EBRT + TMZ	CD3, CD4, CD8, CD19, NK, CD45RA, CCR7, CD25 Baseline, end RT and 1, 3, 5, 7 months post-RT	Decrease in all subsets including Tregs and CD8 cells. Nonsignificant decrease in CD4:CD8 ratio.
Parikh (2014)[32]	22	Oropharynx (HPV+)	EBRT + platinum	CD3, CD4, CD8, Treg, MDSC, PD-1; functional assays Baseline and 3 weeks, 3, 6, and 12 months post-RT	Decrease in all T-cell subsets through 1-year post-RT; increased PD-1 expression on CD4 T cells; decreased HPVE6/7 T cell specific responses in patients who

(*continued on next page*)

Table 2 (*continued*)

Author/year	N	Site	Technique	Markers/Time points	Findings
					initially exhibited such responses; increased MDSC populations
Tang (2017)[33]	35	Metastases	SBRT + ipilimumab	CD4 (regulatory and effector); CD8; 4-1BB, OX40, LAG3, ICOS, GITR, CTLA4, TIM-3, PD-1	Increase in absolute CD8 count and CD8:CD4 ratio associated with clinical benefit from combination ipilimumab/ SBRT.
Gustafson (2017)[34]	10	Liver tumors (metastases/ primary)	SBRT	110 immunophenotypes measured	CD3, CD4 decreased; CD8 stable $CD56^{+}CD16^{+}$ mature (cytotoxic NK) stable $CD56^{br}CD16^{-}$ NK (precursor NK) stable

Abbreviations: brachy = brachytherapy; CD = cluster of differentiation; EBRT= external beam radiation therapy; HPV = human papillomavirus; MDSC = myeloid-derived suppressor cell; NK = natural killer; PD-1 = programmed cell death protein 1; RT = radiation therapy; SBRT = stereotactic body radiation therapy; TMZ = temozolomide; Treg = regulatory T cells.

Nevertheless, the model's basic predictions have been validated by prospective data that show strong correlations between fraction number and field size with RIL risk in patients undergoing stereotactic body RT versus conventional radiation for pancreatic cancer. Moreover, studies in patients with brain tumors and lung cancer showed that the size of various isodose volumes correlated with RIL risk. These studies are summarized in this review.

The first report to correlate radiation field size with severity of lymphopenia and functional immune deficits was published in 2008 based on the study of a small group of patients with breast cancer.[44] In this series, whole breast RT was associated with higher post-RT ALC and natural killer cell activity compared with comprehensive nodal irradiation fields. However, in the absence of detailed volumetric data, the generalizability of this finding is limited.

More recent papers have provided detailed analyses of dosimetric parameters as predictors of lymphopenia risk. The highest-quality data have come from studies on brain tumors, lung cancer, and esophageal carcinoma. Tang et al. reported on the association between field size and acute radiation-induced lymphopenia in a group of 711 patients with non-small cell lung cancer.[10] Gross tumor volume was significantly correlated with lymphocyte nadir, and the volume of the lung that received 5 Gy was the only significant dosimetric predictor of postradiation lymphocyte nadir. The authors reported on a stepwise analysis of multiple lung volume parameters from V5 through V70 in 5-Gy increments and showed that the strength of the correlation between lymphocyte nadir and irradiated lung volume decreased with increasing isodose levels. This finding highlights the extreme radiation sensitivity of lymphocytes, because the cumulative V5 over a 6-week course of RT represents an estimated daily dose of only 0.16 Gy (assuming 30 fractions are delivered).

In patients with high-grade glioma, Huang et al. performed a similar stepwise analysis of dosimetric predictors of postradiation lymphopenia.[6] In this cohort of patients, moderate isodose volumes were found to have the strongest correlation with the risk of severe radiation-induced lymphopenia, with a brain V25 of 65% in patients with grade $\geq$3 lymphopenia compared with 56% in those with grade 0 to 2 lymphopenia ($P = .009$). Brain V25 was also the sole predictive dosimetric factor for severe posttreatment lymphopenia on multivariate analysis.

Further proof of the effects of field size on lymphopenia risk was provided by a study of 210 patients with glioblastoma who were treated with conventional (T1 + T2 magnetic resonance imaging abnormalities + 1.5-2.5 cm margin) versus limited-margin fields (T1 abnormality + 1.8-2 cm margin).[4] Limited-margin radiation was associated with a significant reduction in the planning target volume (PTV) size as well as the brain V25 and, importantly, with a significantly higher median postradiation ALC (1100 vs 900 cells/μL in limited- vs conventional-margin group). In addition, patients treated with limited-margin RT had a lower absolute risk of grade $\geq$3 radiation-induced lymphopenia (16% vs 34%), although this difference was not statistically significant. Grade $\geq$3 lymphopenia at any time point after radiation was independently associated with worse progression-free and overall survival. Although brain V25 was predictive of acute severe lymphopenia risk, the authors did not include V25 as a prognostic factor in the survival analyses.

The unique dosimetric properties of proton beam radiation (PBT) include decreased integral dose as well as large reductions in both entry and exit doses.[45] Therefore,

the use of PBT is a promising strategy to reduce the effective field size and decrease the dose to the circulating immune cells, thereby reducing the risk and severity of radiation-induced lymphopenia. Shiraishi et al. reported on a propensity-matched analysis of lymphopenia risk in a large series of patient with esophageal cancer who were treated with either PBT or photon radiation (136 patients in each arm).[46] The risk of grade 4 lymphopenia was correlated with the log of PTV size in both PBT and photon patients. The use of PBT resulted in a 71% decrease in the risk of grade 4 lymphopenia, adjusted for the effects of age and PTV size.

Stereotactic body RT techniques use both extreme hypofractionation ($\leq$5 fractions) and highly conformal target volumes to deliver an ablative dose of RT. Two recent studies in pancreatic cancer have demonstrated that hypofractionated RT can considerably reduce the risk and severity of radiation-induced lymphopenia. Wild et al. measured post-RT lymphocyte counts in 133 patients with pancreatic cancer treated either with stereotactic body RT (6.6 Gy in 5 fractions) or conventionally fractionated RT (30-54 Gy in 10-30 fractions), and noted both significantly higher median post-treatment ALCs (690 vs 358 cells/μL, $P < .001$) and a lower risk of grade $\geq$3 lymphopenia (14 vs 45%; $P = .007$) in the stereotactic body RT group.[47]

Similarly, Crocenzi et al. showed that, compared with conventional radiation, hypofractionated RT was associated with significantly higher post-treatment ALC as well as higher populations of major lymphocyte subpopulations (including CD4, CD8, CD20, and CD56 cells) throughout nearly 1 year of follow-up after RT for pancreatic cancer.[24]

Conceptual approaches to immune organ-at-risk dosimetry

A robust method to quantify the dose to the immune OAR is essential for the development of effective strategies to prevent or mitigate the risk of treatment-induced lymphopenia in patients who require RT. However, translating the lymphocyte OAR concept for application in the radiation oncology clinic presents unique theoretical and practical challenges because circulating immune cells differ structurally from typical anatomic OARs (eg, kidney or spinal cord) in several key aspects. First, immune cells are not uniformly distributed throughout the body, and cannot be defined by a single anatomic structure or region. In addition, because lymphocytes are in the bloodstream, they are constantly moving through a radiation dose gradient while traversing the irradiated field. Furthermore, circulating immune cells traffic among lymphoid organs and the bloodstream are likely replenished to some extent during treatment, and not all are equally radiation sensitive.[48]

Initial attempts to address the problem of calculating the radiation dose to the circulating immune cells during therapy considered only the dose received by the lymphocytes carried within the bloodstream itself.[43] Such models may be sufficient for the calculation of immune OAR dose in anatomic sites (such as the brain) that lack high concentrations of primary or secondary lymphoid tissues. However, in other body sites and particularly the thorax and abdomen, lymphocyte density within the radiation field varies on the basis of factors other than blood flow rate and volume, and most importantly the distribution of major lymphoid structures (lymphatic vessels and lymph nodes as well as spleen, thymus, and bone marrow) within the treated field.[49] Therefore, an updated method that incorporates estimates of lymphocyte density distribution is required for the most accurate calculation of dose to the immune OAR. The role of lymphocyte-dense organs as major contributors to lymphopenia risk is illustrated by 2 recent studies that implicate spleen dose as a risk factor for RIL in patients receiving upper abdominal RT.

Chadha et al. reported that, among 177 patients who underwent conventionally fractionated RT for pancreatic cancer, the mean spleen dose was highly correlated with the risk of grade $\geq$3 lymphopenia.[16] Of note, low-to-moderate spleen doses (V5 through V20) were more strongly correlated with lymphopenia risk than high doses, and the median cumulative spleen dose of patients with grade $\geq$3 lymphopenia was only 9.8 Gy (0.33 Gy/day for a 30-fraction course), which again illustrates the clinical significance of low-dose volumes in the induction of radiation-induced lymphopenia.

Liu et al. also found that low-dose splenic irradiation was correlated with lymphopenia risk, and reported that mean spleen dose and splenic V5 were predictive of the radiation-induced lymphopenia risk in patients with liver cancer.[50] In this series, the mean spleen dose that predicted severe lymphopenia was also quite low, and patients with a mean spleen dose >2.27 Gy had an approximately 14-fold increase in the risk of severe lymphopenia.

Conceptualizing the dose to the immune OAR in terms of effective field size may assist in resolving some of these difficulties. For the purposes of calculating dose to the lymphocyte OAR, effective field size is expected to be directly proportional to lymphocyte density within the irradiated field, and to the amount of blood passing through the irradiated area, which itself is related to beam-on time (both for individual fractions and total radiation treatment course), target volume, integral dose, and penumbra size. In practical terms, organs that contain very high concentrations of circulating lymphocytes, such as the spleen and thymus, and organs with high blood flow rates (eg, brain, liver, and kidney), would be expected to increase effective field size with respect to lymphopenia risk. Further investigations are needed to

refine and validate this approach to calculating immune OAR dose.

Also, there are significant gaps in our knowledge with regard to the immune system's response to acute and chronic radiation-induced lymphopenia. For example, the kinetics of lymphocyte repopulation after acute radiation-induced lymphodepletion are not well characterized but are of potential importance when attempting to analyze dosimetric predictors of severe lymphopenia. Anatomic inhomogeneities in the distribution of lymphocyte subtypes, which vary in radiation sensitivity, may also affect the accuracy of immune OAR dose calculations.

Conclusions

Radiation-induced lymphopenia has been tied to inferior survival outcomes in a wide variety of treatment-refractory solid tumors. The risk of this common and clinically significant toxicity appears to be directly proportional to the radiation dose received by circulating immune cells during treatment. Although the task of developing robust methods of calculating the immune OAR dose during RT presents considerable theoretical and technical challenges, improving our understanding of immune OAR dosimetry is crucial to identify effective strategies to prevent or mitigating immunosuppression in patients who require RT for cancer. Further research is needed to definitively determine whether correcting or preventing RIL improves survival in solid tumor patients.

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